REMARKS

Claims at Issue. Applicant understands claims 1, 3-9 and 15-27 to be at issue.

Claims Amendments. Claims 1, 8, 9, 17, 21 and 25 have been amended to more clearly state the invention, whereby the modified arginine is specified to be citrulline, and claims 2, 3, 19, 20, 22 and 27 have been cancelled.

New Claims. New claims 28-35 are added by way of amendment, to more precisely state the invention sought to be patented.

Preliminary Issue with Respect to Specifically Claimed Compounds. The Final Office Action Summary clearly states that, among others, claims 3-9 are pending. Claim 4 is direct to a nine specifically identified linear peptides (SEQ ID NO:1 to SEQ ID NO:9). Claim 6 is directed to a specifically disclosed cyclic peptide (SEQ ID NO:10).

No ground of rejection specifically or by implication rejects claim 6. The 35 U.S.C. § 112 rejections specifically excludes claim 6, but inexplicable includes claim 4. The 35 U.S.C. § 102(e) rejection based on Serre et al. does not include either claim 4 or 6. Nowhere in the Final Office Action is there any rejection of claim 6. Further, as argued in the following paragraph, there is no proper rejection of claim 4. Accordingly, it is submitted that claims 4 and 6, based on the Final Office Action, are properly allowable.

The Office Action persists in rejecting claim 4 (but not claim 6) in the 35 U.S.C. § 112 rejection. However, this ground of rejection specifically states that the specification is "enabling for a peptide ... consisting of SEQ ID..." (Page 3 of Detailed Action, First Paragraph, Emphasis in Office Action). Claim 4 was previously amended to state "wherein the peptide consists of a linear peptide..." Similarly, claim 6 was amended to state that "the cyclic peptide consists of SEQ ID..." It is respectfully submitted that, as

amended by the Amendment filed December 4, 2002 (Paper 26), claims 4 and 6 are not properly subject to a 35 U.S.C. § 112 rejection based on the Examiner's own statement in the Detailed Action. Accordingly, claims 4 and 6 are allowable under the rationale advanced in the Office Action. If Applicant has misconstrued the Office Action, it is specifically requested that the Examiner specify the precise grounds on which claims 4 and 6 are rejected.

Claim Objection Issue. On page 4 of the Detailed Action, claim 25 is objected to because of the spelling of the word "cystine". It is assumed that the Examiner intended to object to claim 26, which does contain the word "cystine". It is respectfully submitted that it is "cystine" that was intended and that the word is properly spelled. "Cystine" is commonly recognized in the biochemical and peptide sciences as a dimeric compound formed from two cysteine residues linked by means of a disulfide bond. Indeed, the word "cystine" appears in most standard dictionaries. For the sake of clarity, attached to this Amendment and Response is page 60 from a standard biochemistry textbook, BIOCHEMISTRY, Second Edition, John Wiley & Sons, New York (1995), by Voet and Voet, that discusses cystine and specifically discloses the structure of a "cystine residue." Applicant intends the word "cystine" thus be interpreted and understood in its art-conventional sense. It is noted that the word "cystine" is similarly employed in new claim 31, and the same meaning is intended. It is further noted that page 9 of the specification, lines 31 to 34, discloses "two cysteine residues (c) are bound by means of a sulphur bridge..." This is, as given above, the definition of a cystine.

35 U.S.C. § 112, first paragraph, rejection of Claims 1, 3-5, 7-9, 15-27, Written Description. This ground of rejection is respectfully traversed. It is submitted that the claims, as amended, meet the written description requirement. The claims are specifically amended to be specific for citrulline. The Detailed Action states that "the examiner notes that the disclosed peptides of SEQ ID NOs 7-10 are derived from two areas of one protein (profillagrin) which contains one type of arginine modification

(citrulline)..." (Detailed Action, page 2, last paragraph) It is submitted that the independent claims as now amended are enabled as stated by the Examiner. Specifically, claim 1 is now limited to a peptide derived from profillagrin wherein the arginine modification is a citrulline residue. Similarly, the remaining independent claims are limited to citrulline residues. Accordingly, the claims as amended meet the written description requirement.

It is further noted that claim 21 was and is drawn to a "purified peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1..." This claim is amended to strike the portion of the description relating to "X" in the formula; it is noted that in the sequence listing of record each "Xaa" is defined as "citrulline." Thus SEQ ID NO:1 through SEQ ID NO:10, inclusive, define and are limited to the amino acid sequences containing a citrulline in the Xaa position. As such, it is submitted that there can be no written description objection to these specific peptides, given that they were disclosed in the specification as filed.

35 U.S.C. § 112, first paragraph, rejection of Claims 1, 3- 9 and 15-24, Enablement. This ground of rejection is respectfully traversed. The argument with respect to written description is incorporated by reference.

With specific regard to enablement, it is again noted that the Detailed Action (page 3, second paragraph) specifically states that the specification provides "disclosure of peptides derived from two areas of one protein (profillagrin) which contains one type of arginine modification (citrulline)..." It is submitted that the claims as amended are enabled.

It is further noted that claim 21 was and is drawn to a "purified peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1..." This claim is amended to strike the portion of the description relating to "X" in the formula; it is noted that in the sequence listing of record each "Xaa" is defined as "citrulline." Thus SEQ ID NO:1 through SEQ ID NO:10, inclusive, define and are limited to the amino acid sequences containing a citrulline in the Xaa position. As such, it is submitted that

there can be no enablement objection to these specific peptides, given that they were disclosed in the specification as filed.

Claims 1, 3, 7-9, and 15-20 rejected under 35 U.S.C. § 102(e) as anticipated by Serre et al., U.S. Patent 5,888,833. Applicant respectfully traverses this rejection. Applicant appreciates the argument made by Examiner. However, Applicant notes that the Detailed Action does not address the legal argument raised by Application. For a rejection under 35 U.S.C. § 102(e), the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Anticipation requires that "each element of the claim in issue is found...in a single prior art reference, or that the claimed invention was previously known or embodied in a single prior art device or practice." *Minnesota Mining and Manufacturing Co v. Johnson & Johnson Orthopedics, Inc.* 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992). See generally MPEP § 2131 *et seq.* Tthe question is whether "each and every element as set forth in the claim is found" in Serre et al. Applicant submits that Serre et al. does not disclose "each and every element", either expressly or inherently.

The quotation from Serre et al. at column 5, lines 15-24, describes the use of certain rat esophagus antigens for the detection of antibodies from patients with rheumatoid arthritis. These antigens are characterized by their apparent molecular weight upon SDS-PAGE and found to consist of three different fractions; see col. 5, line 45 to col. 6, line 21. These antigens were found to be cross-reactive with human fillagrin; see col. 6, lines 24-28. Based upon this observation, Serre et al. propose to use fillagrin, profillagrin, the fractions thereof or the peptide fragments thereof for the in vitro diagnosis of rheumatoid arthritis. Col. 8, line 20-22. Serre et al. thus describe an inhomogeneous preparation of fillagrin and profillagrin and peptides derived therefrom. It is noted that it was known in the art at that time

that the sequences of profillagrin and fillagrin differ greatly even within a single individual. See, e.g., Gan et al., *Biochemistry* 29:9432-9440 (1990).

The claims as amended, and new claims 28-35, are directed to subject matter that is clearly novel over Serre et al. since the claims are drawn to a "purified peptide", as opposed to the inhomogenous mixture disclosed by Serre et al. There is no teaching, expressly or by implication, in Serre et al. of a "purified peptide" meeting the specific limitations of the independent claims (derived from profillagrin and including a citrulline). Serre et al. does disclose, as noted by the Examiner, that peptide fragments may be obtained. See column 7, lines 36-67. However, this merely teaches art-conventional methods of making peptides, such as proteolysis of antigen proteins (col. 7, lines 40-41), making synthetic peptides (col. 7, line 48) or making genetically engineered peptides (col. 7, line 49). However, at most Serre et al. teach that a random selection of peptides derived from a mixture of fillagrin molecules may be used in the diagnosis of rheumatoid arthritis. Specifically, Serre et al. fails to teach that a purified peptide derived from profillagrin and/or fillagrin is especially useful in the diagnosis of rheumatoid arthritis when it includes at least one citrulline residue. It is this point to which the claims, as amended, are directed.

It may be that Serre et al. also recognized that profillagrin undergoes a maturation during which basic arginine residues are converted to neutral citrulline residues. However, Serre et al. mention this only in the context of explaining why their rat esophagus preparation lacks homogeneity. (Col. 5, lines 21-24). Serre et al. thus simply teach that their mixture of proteins contain citrulline residues. In no way is it described in Serre et al. that a citrulline residue is essential for immunoreactivity. To argue anticipation, or indeed obviousness, based on Serre et al. in an *ex post facto* analysis that can only be sustained with the benefit of the knowledge of Applicant's invention. In simplest terms, Serre et al. recognize that arginine can be converted to citrulline in filaggrin. However, Serre et al. note this only in the context of explaining the lack of homogeneity which results in several isoelectric variants for the same molecular weight. Serre et al. also mention that "peptides" can be made, such as by proteolysis or synthesis. However, Serre et al. never claim or describe that the citrulline is essential for immunoreactivity, or that a peptide must include

the citrulline in order to be immunoreactive. Serre et al. merely describe the presence of citrulline, without ever teaching or suggesting that it is only peptides with citrulline which are immunoreactive. In colloquial terms, Serre et al. were moving in the right direction, but failed to either expressly or by implication make the final and necessary connection -- that a peptide must have citrulline in order to be immunoreactive. It is noted that Serre et al. disclose absolutely no peptides; they merely disclose a possibility of peptides, but do not ever define any peptide. It is further noted that the antigenic proteins disclosed by Serre et al. have a high molecular weight. Obviously there exist an incredible number of peptides with "at least 6 amino acids" (col. 7, line 46) that will not contain citrulline. In the absence of absolutely any teaching in Serre et al. that a peptide must include "a citrulline residue" (see claim 1 as amended), it cannot fairly be said that Serre et al. discloses "each and every element as set forth in the claim." Accordingly, Serre et al. does not anticipate the claims as amended.

Claims 25-27 are rejected under 35 U.S.C. § 103(a) over Serre et al. in view of Greene. For the reasons given above with respect to Serre et al., Applicant respectfully traverses this ground of rejection.

New Claims. For the reasons given above, it is submitted that the new claims are free from any basis of rejection heretofore asserted. It is also further noted that claims 29 and 32 are directed to specific peptides identified by SEQ ID NO., and that no prior art teaches, suggests or makes obvious such peptides.

Conclusion. In view of the above amendments and remarks, it is respectfully submitted that all grounds of rejection and objection have been avoided and/or traversed. It is believed that the case is now in condition for allowance and same is respectfully requested.

If any issues remain, or if the Examiner believes that prosecution of this application might be expedited by discussion of the issues, she is cordially invited to telephone the undersigned attorney for Applicants at the telephone number listed below.

Authorization is given to charge payment of any additional claims or other fees required, or credit any overpayment, to Deposit Acct. 13-4213. A duplicate of this paper is enclosed for accounting purposes.

Respectfully submitted,

By: _____
Stephen A. Slusher, Reg. No. 43,924
Direct line: (505) 998-6130

PEACOCK, MYERS & ADAMS, P.C.
Attorneys for Applicant(s)
P.O. BOX 26927
Albuquerque, New Mexico 87125-6927

Telephone: (505) 998-1500
Facsimile: (505) 243-2542

Customer No. 005179

Attachment: Excerpt at page 60 from *Biochemistry, Second Ed.*, Donald Voet, et al., John Wiley & Sons, Inc., (1995)

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DONALD VOET
University of Pennsylvania
JUDITH G. VOET
Swarthmore College

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C. Classification and Characteristics

The most common and perhaps the most useful way of classifying the 20 "standard" amino acids is according to the polarities of their side chains (R groups). This is because proteins fold to their native conformations largely in response to the tendency to remove their hydrophobic side chains from contact with water and to solvate their hydrophilic side chains (Chapters 7 and 8). According to this classification scheme, there are three major types of amino acids: (1) those with nonpolar R groups, (2) those with uncharged polar R groups, and (3) those with charged polar R groups.

The Nonpolar Amino Acid Side Chains Have a Variety of Shapes and Sizes

Nine amino acids are classified as having nonpolar side chains. **Glycine** (which, when it was found to be a component of gelatin in 1820, was the first amino acid to be identified in protein hydrolyzates) has the smallest possible side chain, an H atom. **Alanine, valine, leucine,** and **isoleucine** have aliphatic hydrocarbon side chains ranging in size from a methyl group for alanine to isomeric butyl groups for leucine and isoleucine. **Methionine** has a thiol ether side chain that resembles an *n*-butyl group in many of its physical properties (C and S have nearly equal electronegativities and S is about the size of a methylene group). **Proline**, a cyclic secondary amino acid, has conformational constraints imposed by the cyclic nature of its pyrrolidine side group, which is unique among the "standard" 20 amino acids. **Phenylalanine**, with its phenyl moiety, and **tryptophan** with its indole group, contain aromatic side groups, which are characterized by bulk as well as nonpolarity.

Uncharged Polar Side Chains Have Hydroxyl, Amide, or Thiol Groups

Six amino acids are commonly classified as having uncharged polar side chains. **Serine** and **threonine** bear hydroxylic R groups of different sizes. **Asparagine** and **glutamine** have amide-bearing side chains of different sizes. **Tyrosine** has a phenolic group, which, together with the aromatic groups of phenylalanine and tryptophan, accounts for most of the UV absorbance and fluoresence exhibited by proteins. **Cysteine** has a thiol group that is unique among the 20 amino acids in that it often forms a disulfide bond to another cysteine residue (Fig. 4-4) through the oxidation of their thiol groups. This dimeric compound is referred to in the older biochemical literature as the amino acid **cystine**. The disulfide bond has great importance in protein structure: *It can join separate polypeptide chains or cross-link two cysteines in the same chain.* The confusing similarity between the names cysteine and cystine has led to the former occasionally being referred to as a half-cystine residue. However, the realization that cystine arises through the cross-linking of two cysteine residues after polypeptide biosynthesis has occurred has caused the name cystine to become less commonly used.

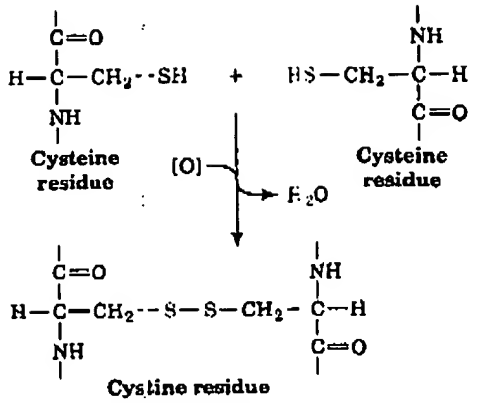

FIGURE 4-4. The cystine residue consists of two disulfide-linked cysteine residues.

Charged Polar Side Chains May Be Positively or Negatively Charged

Five amino acids have charged side chains. The basic amino acids are positively charged at physiological pH values; they are **lysine**, which has a butylammonium side chain, **arginine**, which bears a guanidino group, and **histidine**, which carries an imidazolium moiety. Of the 20 α-amino acids, only histidine, with $pK_R = 6.0$, ionizes within the physiological pH range. At pH 6.0, its imidazole side group is only 50% charged so that histidine is neutral at the basic end of the physiological pH range. As a consequence, histidine side chains often participate in the catalytic reactions of enzymes. The acidic amino acids, **aspartic acid** and **glutamic acid**, are negatively charged above pH 3; in their ionized state, they are often referred to as **aspartate** and **glutamate**. Asparagine and glutamine are, respectively, the amides of aspartic acid and glutamic acid.

The allocation of the 20 amino acids among the three different groups is, of course, rather arbitrary. For example, glycine and alanine, the smallest of the amino acids, and tryptophan, with its heterocyclic ring, might just as well be classified as uncharged polar amino acids. Similarly, tyrosine and cysteine, with their ionizable side chains, might also be thought of as charged polar amino acids, particularly at higher pH values, whereas asparagine and glutamine are nearly as polar as their corresponding carboxylates, aspartate and glutamate.

The 20 amino acids vary considerably in their physicochemical properties such as polarity, acidity, basicity, aromaticity, bulk, conformational flexibility, ability to cross-link, ability to hydrogen bond, and chemical reactivity. These several characteristics, many of which are interrelated, are largely responsible for proteins' great range of properties.